REMARKS

1. Election/Restriction

Applicants acknowledge that the restriction requirement has been made final and that prosecution of elected claims 1-51 will proceed.

2. Rejection for Indefiniteness (35 U.S.C. §112, 2nd Paragraph)

Claims 1-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the Office Action (pages 2-3), the Examiner stated:

> Claim 1 is rejected over the recitation of the phrase, "introduction of intermediate structure". It is not clear if the structure present in the nucleic acid to be produced is claimed or a helper molecular for the production of nucleic acid is claimed or a molecular structure in between the above mentioned molecules are claimed. It is not clear what are the phases between which the claimed intermediate structure belongs. The metes and bounds of the claim is vague and indefinite.

In response, Applicants respectfully point out that the subject matter of "intermediate structures" is thoroughly discussed in their specification, beginning with the "Background of the Invention" on pages 1-4. Additional disclosure on "intermediate structures" continues in the "Detailed Description of the Invention" on page 13.

More particularly, in the Background of the Invention two examples of prior art were cited by Applicants and discussed. These examples involved and required the "introduction of an intermediate structure."

Example 1 The 3SR system described by Guatelli et al., 1990 and NASBA disclosed by Malek in US patent No. 5,130,238 were described by Applicants in the specification as follows:

> **These procedures rely on the formation of a new "intermediate structure"....**
>
> **For the intermediate construct formation, the primer must contain the promoter for the DNA dependent RNA polymerase.**

In these particular cases, two different types of intermediate structures can be observed. First, these systems depend upon the introduction of an exogenous RNA polymerase sequence for synthesis of RNA. Second, these systems cycle between a double-stranded DNA molecule which makes RNA strands which in turn are used to make double-stranded DNA strands etc. The double-stranded DNA is clearly an intermediate structure used to make RNA or conversely, the RNA is an intermediate structure used for making double-stranded DNA.

Example 2 The SDA system disclosed by Walker et al., in various European patent applications was described in the specification as follows:

> **The intermediate structure of this procedure is formed by the introduction of an artificial sequence not present in the specific target nucleic acid and which is required for the asymmetric recognition site of the restriction enzyme.**

To paraphrase the quotation above, this SDA system depends upon the introduction of an artificial exogeneous restriction enzyme sequence As such, the specification gives meaning to the phrase "intermediate structure" as being artificially introduced sequences that form enzyme recognition sites for enzymatic action that result in the production of multiple copies of a desirable sequence. It should be pointed out that in both of the examples cited above we are describing requirements in that neither of these systems would work without the presence of either the RNA polymerase promoter (3SR + NASBA) or restriction sites (SDA) that each system employs.

It is believed that the phrase "introduction of intermediate structure" is sufficiently clear so that a person skilled in the art could readily comprehend the metes and bounds of the language in claim 1.

In view of the foregoing remarks and explanation regarding the phrase "introduction of intermediate structure," Applicants respectfully request reconsideration and withdrawal of the indefiniteness rejection.

Commonality of Ownership

Applicants affirm that the inventorship and invention dates of each claim in this application was commonly owned.

3. Rejection for Anticipation (35 U.S.C. §102)

Claims 1-6, 8-9, 14-15, 18-21, 26 and 28-29 stand rejected under 35 U.S.C. 102 (b) as being anticipated by Kacian et al. (U.S. Patent 5,399,491) (March 21, 1995). In the Office Action (pages 3-5), the Examiner stated:

Kacian et al teach an in vitro process for producing more than one copy of a specific nucleic acid, the process being independent of a requirement for the introduction of an intermediate structure for the production of the specific nucleic acid (Abstract and Figure 1J and Column 17, lines 34-38), the process comprising the steps of:

a) providing a nucleic acid sample containing or suspected of containing the sequence of the specific nucleic acid (Abstract, Figure 1J and Column 17, lines 34-38);

b) contacting the sample with a mixture comprising:

(i) nucleic acid precursors (Figure 1J and Column 17, lines 34-38),

(ii) one or more specific nucleic acid primers each of which is complementary to a distinct sequence of the specific nucleic acid (Figure 1J and Column 17, lines 34-38), and

(iii) an effective amount of a nucleic acid producing catalyst (Figure 1J and Column 17, lines 34-38); and

c) allowing the mixture to react under isostatic conditions of temperature, buffer and ionic strength, thereby producing more than one copy of the specific nucleic acid (Figure 1J and Column 17, lines 34-38 and Abstract).

i Kacian et al teach an in vitro process wherein the specific nucleic acid is single-stranded (Figure IJ and Column 17, lines 34-38).

Kacian et al teach an in vitro process wherein the specific nucleic acid is ribonucleic acid.(Figure 1J).

Kacian et al teach an in vitro process wherein the specific nucleic acid is in solution (Column 25, lines 44-60).

Kacian et al teach an in vitro process further comprising the step of treating the specific nucleic acid with a blunt-end promoting restriction enzyme (Figure 1 J).

Kacian et al teach an in vitro process wherein the specific nucleic acid is isolated prior to the contacting step (b) (Figure I J).

Kacian et al teach an in vitro process wherein the captured nucleic acid is carried out by restriction enzyme (Figure 1 J).

Kacian et al teach an in vitro process wherein the specific nucleic acid primers is deoxyribonucleic acid (Figure 1 J).

Kacian et al teach an in vitro process wherein the specific nucleic acid primers contain no more than five complementary base pairs and comprise from about 5 to 100 nucleotides (Column 24, lines 52-63).

Kacian et al teach an in vitro process wherein the nucleic acid producing catalyst is selected from DNA polymerase and reverse transcriptase (Figure 1J).
Kacian et al teach an in vitro process further comprising the step (d) of detecting the product produced in step c) (Figures 6a and 66).
Kacian et al teach an in vitro process wherein the detecting step is carried out by means of incorporating into the product a labeled primer (Figures 6a and 6b).

The anticipation rejection is respectfully traversed.
In response, Applicants point out It should be pointed out that the invention disclosed by Kacian etal. is a variation of the 3SR and NASBA systems that were described in the specification and discussed *supra*. This system has an absolute requirement for the introduction of an artificial RNA polymerase promoter sequence to synthesize multiple copies of a target organism. It should also be ponted out that due to the nature of this system, Kacian et al., do **not** "teach a process wherein the nucleic acid producing catalyst is selected from DNA polymerase and reverse transcriptase." Instead, they have an additional requirement of the presence of an RNA polymerase as well.

4. **First Rejection for Obviousness (35 U.S.C. §103(a))**

Claims 1-9, 14-15, 18-21, 26 and 28-29 stand rejected under 35 U.S.C. 103 (a) over Kacian et al. (U.S. Patent 5,399,491) (March 21, 1995) in view of Bernstein et al. (U.S. Patent 6,183,961 B 1) (February 6, 2001). In the Office Action (pages 6-7), the Examiner stated:

Kacian et al teach the method of claims 1-6, 8-9, 14-15, 18-21, 26 anal 28-29 as described above.
Kacian et al do not teach the process wherein the isolation of specific nucleic acid is carried out by means of sandwich capture.
Bernstein et al. teach the process wherein the isolation of specific nucleic acid is carried out by means of sandwich capture. (Column 16, lines 52-56).
It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the sandwich capture of Bernstein et al, into the method of Kacian et al., since Bernstein et al. state, "For example, sandwich assays are commercially useful hybridization assays for detecting or isolating nucleic acid sequences (Column 16, lines 52-54)." An ordinary practitioner would have been motivated to combine and

substitute the sandwich capture of Bernstein et al. into the method of Kacian et al ., in order to achieve the express advantages , as noted by Bernstein et al., of an assay which is commercially useful hybridization assay for detecting or isolating nucleic acid sequences.

The obviousness rejection is respectfully traversed.

In response, Applicants respectfully point out that the combination of Kacian and Bernstein and the proposed substitution of the sandwich capture method of Bernstein et al. into the method of Kacian et al. would not have produced the present invention. Such a combined reading of the two cited documents and the proposed substitution would still have not eliminated Kacian's requirement for the formation of an intermediate structure of an artificially added RNA promoter. The present claims eschew the formation of any intermediate structures.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

5. Second Rejection for Obviousness (35 U.S.C. §103(a))

Claims 1-6, 8-9, 14-15, 18-21, 26 , 28-35, and 39-42 stand rejected under 35 U.S.C. 103(a) over Kacian et al. (U.S. Patent 5,399,491) (March 21, 1995) in view of Jones (U.S. Patent 6,190,889 B1) (February 20, 2001). In the Office Action (pages 7-8), the Examiner stated:

> Kacian et al teach an in vitro process of claims 1-6, 8-9, 14-15, 18-21, 26 and 28-29 as described above including the enzyme ribonuclease H.
>
> Kacian et al do not teach an in vitro process for producing more than one copy of a specific nucleic acid, the products being substantially free of any primer-coded sequences by using chemically modified primers and removing substantially or all primer-coded sequences from the product produced in step to regenerate a primer binding site, thereby allowing a new priming event to occur and producing more than one copy of the specific nucleic acid.
>
> Jones teaches an in vitro process for producing more than one copy of a specific nucleic acid, the products being substantially free of any primer-coded sequences using chemically modified deoxyribonucleic acid primers and removing substantially or all primer-coded sequences from the product produced in step to regenerate a primer binding site, thereby allowing a new priming event to occur and producing more than one copy of the specific nucleic acid (Abstract and Claim 1).

Kacian et al do not teach an in vitro process wherein the removing is carried by digestion with. an enzyme.

Jones teaches an in vitro process wherein the removing is carried by digestion with an enzyme.(Claims 1 and 2).

Kacian et al do not teach an in vitro process wherein a primer binding site is regenerated, thereby allowing a new priming event to occur and producing more than one copy of the specific nucleic acid.

Jones teaches an in vitro process wherein a primer binding site is regenerated, thereby allowing a new priming event to occur and producing more than one copy of the specific nucleic acid. (Column 42, line 46 to column 43, line 31).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the method for removing primer sequences of Jones into the method of Kacian et al., since Jones states, "Thus, the invention pertains to novel methods for generating staggered templates *and for* iterative and regenerative DNA sequencing as well as to methods for automated DNA sequencing (Column 4, lines 37-40)." An ordinary practitioner would have been motivated to combine and substitute the method for removing primer sequences of Jones into the method of Kacian et al.. in order to achieve the express advantages , as noted by Jones., of an invention that pertains to novel methods for generating staggered templates *and* for iterative and regenerative DNA sequencing as well as to methods for automated DNA sequencing.

The second rejection for obviousness is respectfully traversed.

In response, Applicants respectfully point out that as in the case of Kacian's disclosure, Jones also teaches the introduction of an intermediate structure since he utilizes the ligation of an segment that contains a) an artificial primer binding site and b) an artificial restriction enzymes site. Additionally, Jones does not teach the generation of products that are substantially free of any primer-coded sequences since his objective is clearly to produce nucleic acid sequences that will be detectable by labels in the primers used for extension reactions.

In light of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the second obviousness rejection.

6. Third Rejection for Obviousness (35 U.S.C. §103(a))

Claims *1-6 and* 8-46 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kacian et al. (U.S. Patent 5,399,491) (March 21, 1995) in view of Jones (U.S. Patent 6,190,889 B I) (February 20, 2001) further in view of Ward

et al. (U.S. Patent 4,711,955) (December 8, 1987). In the Office Action (pages 9-11), the Examiner stated:

> Kacian et al in view of Jones teach the in vitro process of claims 1-6, 8-9, 14-1 S, 18-21, 26 , 28-35, and 39-42 as described above.
>
> Kacian et al in view of Jones do not teach the process wherein at least one modified nucleotide or nucleotide analog selected from cytidine S'-triphosphate or deoxy cytidine S'triphosphate.
>
> Ward et al teach the process wherein at least one modified nucleotide or nucleotide analog selected from cytidine 5'-triphosphate or deoxy cytidine S'-triphosphate (Column 3, lines 20-39 and Examples 3 and 4).
>
> Kacim et al in view of Jones do not teach the process wherein the analog is modified on the sugar.
>
> Ward et al teach the process wherein the analog is modified on the sugar (Abstract and Column 3, lines 20-39).
>
> Kacian et al in view of Jones do not teach the process wherein the analogs comprise from about 1 to about 200 nucleotide.
>
> Ward et al. teaches the process wherein the analogs comprise from about 1 to about 200 nucleotide. (Column S, line 1 to Column 6, line 32).
>
> Kacian et al in view of Jones do not teach the process wherein the base sequences are linked together by other than a phosphodiester bond.
>
> Ward et al. teaches the process wherein the base sequences are linked together by other than a phosphodiester bond, (Claim 8).
>
> It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the modified nucleotide or nucleotide analog of Ward et al. into the nucleic acid sequence amplification method of Kacian et al in view of Jones, since Ward et al. state, "The interaction between modified nucleotides and specific proteins can be utilized as an alternative to radioisotopes for the detection and localization of nucleic acid components in many of the procedures currently used in biomedical and recombinant-DNA technologies. Methods employing these modified nucleotide-protein interactions have detection capacities equal to or greater than procedures which utilize radioisotopes and they often can be performed more rapidly and with greater resolving power. These new nucleotide derivatives can be prepared relatively inexpensively by chemical procedures which have

been developed and standardized as discussed more fully hereinafter. More significantly, since neither the nucleotide probes of this invention nor the protein reagents employed with them are radioactive, the compounds can be prepared, utilized and disposed of without the elaborate safety procedures required for radioisotopic protocols. Moreover, these nucleotide derivatives are chemically stable and can be expected to have functional shelf-lives of several years or more. Finally, these compounds permit the development of safer, more economical, more rapid, and more reproducible research and diagnostic procedures (Column 2, line 59 to column 3, line 17)." An ordinary practitioner would have been motivated to combine and substitute the modified nucleotide or nucleotide analog of Ward et al, into the nucleic acid sequence amplification method of Kacian et al in view of Jones , in order to achieve the express advantages, as noted by Ward et al, of a method which permit the development of safer, more economical, more rapid, and more reproducible research and diagnostic procedures.

The third obviousness rejection is respectfully traversed.

In response, Applicants are mindful that the combination or addition of Ward's to Kacian would still not have produced the present invention since Ward would not have eliminated Kacian's requirement for the formation of an intermediate structure of an artificially added RNA promoter.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the third obviousness rejection.

7. Fourth Rejection for Obviousness (35 U.S.C. §103(a))

Claims 1-6 and 8-51 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kacian et al. (U.S. Patent 5,399,491) (March 21, 1995) in view of Jones (U.S. Patent 6,190,889 BI) (February 20, 2001) further in view of Ward et al. (U.S. Patent 4,711,955) (December 8, 1987) further in view of Dahlberg et al. (U.S. Patent 5,871,911) (February 16, 1999). In the Office Action (pages 11-12), the Examiner stated:

> Kacian et al. in view of Jones further in view of Ward et al. teach the method of claims 1-46 as described above.
>
> Kacian et al. in view of Jones further in view of Ward et al do not teach one or more specific unmodified primers comprising at least one non-complimentary sequence to a distinct sequence of the specific nucleic acid, such that upon hybridization to the specific nucleic acid at least one loop structure is formed.

Dahlberg et al teach one or more specific unmodified primers comprising at least one non-complimentary sequence to a distinct sequence of the specific nucleic acid, such that upon hybridization to the specific nucleic acid at least one loop structure is formed. (Figure 3, Column 6, line 60 to Column 7, line 5).

It would have bean prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the primer having loop structure of Dahlberg et al. into the method of Kacian et al. in view of Ward et al ., since Dahlberg et al. state, "In this case, the pilot oligonucleotide has a 3' terminal hairpin that acts as an integral primer. The looped end of the hairpin may be of a specific sequence called a tetra-loop, which confers extraordinary thermostability on the stem-loop structure (Column 6, lines 61-65)." An ordinary practitioner would have been motivated to combine and substitute the primer having loop structure of Dahlberg et al, into the method of Kacian et al. in view of Ward et al. in order to achieve the express advantages, as noted by Dahlberg et al., of a looped end primer which confers extraordinary thermostability on the stem-loop structure.

The fourth obviousness rejection is respectfully traversed.

In response, Applicants respectfully point out that there are two significant reasons why the fourth obviousness rejection does not survive scrutiny. First, the combination of Kacian and Dahlberg would still not have produced the present invention, since Dahlberg would not eliminate Kacian's requirement for the formation of an intermediate structure of an artificially added RNA promoter. Second, the invention described by Dahlberg does not seem to regenerate a primer binding site since the enzyme activity is specifically directed to the sites on the target molecule where primers are not homologous to the primer.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the fourth obviousness rejection.

Favorable action on the merits is respectfully urged.

* * * * * * *

SUMMARY AND CONCLUSIONS

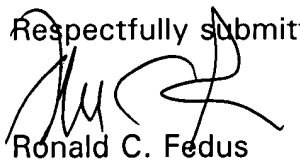
No claims have been added, canceled or amended by this paper.

No claim fee or fees are believed due.

In the event that any fee is due for this paper or any paper being filed in connection with the accompanying Petition, The Patent and Trademark Office is authorized to charge any such fee or fees to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that he be contacted at the number provided below.

Respectfully submitted,



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